



UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM — MINORITY STAFF
SPECIAL INVESTIGATIONS DIVISION
JUNE 2006

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Prescription for Harm
The Decline in
FDA Enforcement Activity

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PREPARED FOR
REP. HENRY A. WAXMAN

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EXECUTIVE SUMMARY

The U.S. Food and Drug Administration was created 100 years ago to protect the public from dangerous food and drugs. From its inception as the Bureau of Chemistry within the Department of Agriculture, enforcement actions against purveyors of contaminated or unsafe products played a central role in the agency's effectiveness. According to former Commissioner David Kessler, "FDA *must* stand for, it *must* embody, strong and judicious enforcement."

At the request of Rep. Henry A. Waxman, this report examines how the Bush Administration has carried out FDA's historic enforcement responsibilities. The report is the result of a 15-month investigation that included a review of thousands of pages of internal agency enforcement records. It finds that there has been a precipitous drop in FDA enforcement actions over the last five years. In some cases, FDA headquarters rejected the enforcement recommendations of FDA field offices despite findings by agency inspectors that violations led to multiple deaths or serious injuries.

Independent experts consulted during the preparation of this report describe the agency's enforcement efforts as being in severe decline. According to Dr. Jerry Avorn of the Harvard Medical School, there is "a growing laxity in FDA's surveillance and enforcement procedures," a "dangerous decline in regulatory vigilance," and an "obvious unwillingness to move forward even on claims from its own field offices." Dr. Michael Wilkes of the University of California, Davis, School of Medicine said that the agency has "systematically ignored District Field Officers and regularly overridden their explicit and well documented concerns about drug safety and public health." Sammie Young, a former senior FDA enforcement official, expressed "serious concerns about how FDA is fulfilling its enforcement responsibilities."

Key Findings

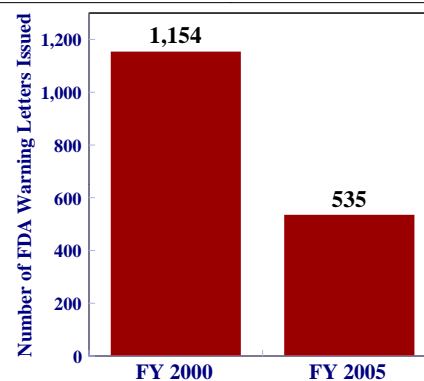
FDA enforcement actions have declined under the Bush Administration.

The number of warning letters issued by the agency for violations of federal requirements has fallen by over 50%, from 1,154 in 2000 to 535 in 2005, a 15-year low. During the same period, the number of seizures of mislabeled, defective, and dangerous products has declined by 44%.

Every center within FDA has experienced a decline in enforcement. The largest drop in warning letters occurred at the Center on Devices and Radiological Health, which is responsible for ensuring the safety of medical devices. Despite growing reports of malfunctions in medical devices such as pacemakers and defibrillators, the Center on Devices issued 65% fewer warning letters in 2005 than in 2000.

The decline in enforcement does not appear to be the result of increased compliance by manufacturers. The number of violations by food and drug manufacturers observed by FDA agents during field inspections has remained relatively constant.

FDA Enforcement Has Declined by Over 50% Since 2000



FDA headquarters officials have routinely rejected the enforcement recommendations of career field staff. Internal agency documents show that in at least 138 cases over the last five years

involving drugs and biological products, FDA failed to take enforcement actions despite receiving recommendations from agency field inspectors describing violations of FDA requirements.

In one case documented in internal agency files, a medical supply firm in Ohio sold a tank of nitrogen gas as medical oxygen, causing the death of four nursing home residents and injuring six others. The Cincinnati district office recommended that FDA initiate criminal proceedings after finding that the deaths and injuries were “directly attributable to” the firm’s violation of FDA standards. FDA headquarters did not act on the recommendation for nearly 18 months. Two and a half years after the district’s recommendation, FDA closed the case without taking any enforcement action.

Internal agency files disclose multiple similar cases where FDA field inspectors found serious violations that caused or threatened death or serious injury, but FDA headquarters rejected the recommendations for enforcement action. For example:

- FDA field inspectors in Puerto Rico reported “significant objectionable conditions” at a blood bank that resulted in one death and multiple patients receiving the wrong blood products. FDA headquarters rejected the recommendation for issuance of a warning letter, called the death “a single, isolated event,” and took no enforcement action.
- FDA field inspectors in Colorado recommended that FDA issue a warning letter to the manufacturer of a “hangover formula” that sent several individuals to the emergency room and contained “a

toxic level of caffeine.” FDA headquarters took no action.

- FDA field inspectors in Connecticut documented that a drug manufacturer failed “to report twelve serious and unexpected adverse events,” including convulsions and loss of consciousness, caused by its product during a three-month period. FDA headquarters rejected the recommendation for issuance of a warning letter, sending the manufacturer an “untitled” letter instead.

FDA’s recordkeeping and case tracking practices are inadequate.

Although the Federal Records Act and internal agency procedures require FDA to keep records that document agency enforcement decisions, FDA does not appear to comply with these requirements. FDA’s response to Committee requests for relevant enforcement documents was haphazard, incomplete, and untimely. FDA officials explained that FDA could not provide prompt and complete responses because the agency lacks a system that enables it to track enforcement recommendations from field offices.

According to Dr. Avorn, FDA was once “the most vigilant drug regulatory body in the world.” But as FDA reaches its centennial, the agency’s historic commitment to enforcement is increasingly in doubt. Over the past five years, FDA enforcement actions have declined across all divisions as officials in Washington have repeatedly turned away calls by agency field staff for vigorous enforcement action.

BACKGROUND

One hundred years ago on June 30, 1906, President Theodore Roosevelt signed the Pure Food and Drug Act into law in response to growing threats from contaminated food and dangerous or ineffective drugs. The 1906 law directed the Bureau of Chemistry in the Department of Agriculture — the agency destined to become the modern Food and Drug Administration — to prevent the manufacture, sale, or transportation of food and drugs that were unsafe, impure, or ineffective.

The creation of the FDA marked a historic moment for the federal government. As FDA historian Philip Hilts wrote:

The change in policy that came with this law was a fundamental one. It was an assertion that it was the job of government to protect citizens from some kinds of commerce rather than just to protect commerce. ... [I]t acknowledged that there are instances, such as the ensuring of a supply of safe and wholesome food and medicine for the nation, in which the government must protect citizens against business.¹

From the outset, enforcement played a critical role in the agency's success. The 1906 Act gave the agency the authority to seek criminal penalties, including fines and imprisonment, for serious violations. The agency's first head, Harvey Wiley, used this authority to pursue high-profile prosecutions, initiating cases against a meat plant that used dead horses to make "beef" and food processors that used rotten tomatoes to make "ketchup."²

FDA's enforcement authorities were significantly strengthened in 1938 when Congress passed the Federal Food, Drug, and Cosmetic Act. This law gave FDA express authority to inspect manufacturing facilities and added injunctions to the agency's enforcement tools.³ The law was later amended to provide even stronger tools for enforcement, such as allowing investigators greater access to company records.⁴

The modern FDA regulates food, drugs, biological products like vaccines, medical devices, cosmetics, and dietary supplements to protect the public from dangerous products and misleading claims. The degree of FDA regulation depends on the product being regulated. In the case of drugs, biological products, and medical devices, FDA requires manufacturers to prove that their products are safe and effective and to adhere to

¹ Philip J. Hilts, *Protecting America's Health*, at 55 (2003).

² *Id.* at 57-58 (2003).

³ John P. Swann, FDA History Office, *History of the FDA* (1998) (online at <http://www.fda.gov/oc/history/historyoffda/default.htm>).

⁴ *Id.*

“good manufacturing practices” in the production process. Manufacturers of dietary supplements generally do not have to prove that their products are safe or effective, but they are subject to regulations that prohibit the distribution of dangerous products. Foods are regulated by FDA to ensure that they do not contain poisonous or dangerous substances that might make them harmful to health. And virtually all manufacturers of FDA-regulated products are subject to statutory prohibitions on making false or misleading claims about their products.

FDA uses a variety of tools and authorities to enforce these legal requirements. FDA has 19 district offices around the country. One of their primary functions is to conduct inspections of manufacturing facilities to assess compliance with FDA standards. By law, FDA is supposed to inspect drug, biological product, and device facilities every two years.⁵ But this level of inspection is rarely achieved. In some cases, up to six years pass between FDA inspections of facilities.⁶

When a violation of FDA standards is documented during an inspection, FDA has several options. If the violation is serious, FDA has statutory authority to seize or recall products,⁷ impose civil fines,⁸ or initiate criminal action.⁹

More typically, FDA will send the manufacturer either a “warning letter” or a “notice of violation,” which is also called an “untitled letter.” A warning letter notifies a firm of violations, requires a written response, and warns that failure to correct the violations can be expected to lead to additional enforcement action. Under FDA’s enforcement procedures, the agency also must evaluate the firm’s response to determine whether the violations cited in the warning letter have been corrected. If the firm’s response is inadequate, FDA must take other enforcement action “as necessary to achieve correction.”¹⁰

An untitled letter is a significantly less serious step. It informs a firm of observed violations but does not require a written response or warn that enforcement action may ensue if violations are not corrected. Unlike a warning letter, an untitled letter also does not prompt a mandatory FDA follow-up.¹¹

⁵ Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §360(h); 21 C.F.R. §600.21.

⁶ *Bausch & Lomb Not Inspected Since '03*, Atlanta Journal and Constitution (Apr. 21, 2006) (“FDA manages to inspect plants only about once every five or six years, sometimes even less often, according to agency officials and budget documents”). See also Government Accountability Office, *Overseeing the U.S. Food Supply: Steps Should be Taken to Reduce Overlapping Inspections and Related Activities*, 9 (May 17, 2005) (FDA inspects food facilities “with a frequency ranging from 1 to 5 years”).

⁷ 21 U.S.C. §334.

⁸ 21 U.S.C. §303.

⁹ *Id.*

¹⁰ FDA, *Regulatory Procedures Manual*, Chapter 4 (March 2004).

¹¹ FDA, *Regulatory Procedures Manual*, Chapter 4 (March 2004); FDA, *The Enforcement Story, Fiscal Year 2005*, at 9-2.

If a firm receives a warning letter but does not remedy the violation, FDA can invoke a range of enforcement responses, including seizure, injunction, recall, or civil or criminal action. Injunctions and civil penalties are rare, with fewer than 15 injunctions and only one or two civil penalties imposed each year.¹²

Vigorous enforcement by FDA through inspections, warning letters, seizures, injunctions, and civil and criminal actions is essential to FDA's mission. Effective and even-handed enforcement removes dangerous products from the market, deters future violations, and provides a level playing field for companies with strong safety records, ensuring that those who operate safely are not forced to compete with those who do not. As former FDA Commissioner David Kessler wrote:

The FDA is the regulator ... The FDA *must* stand for, it *must* embody, strong and judicious enforcement.¹³

¹² FDA, *The Enforcement Story, Fiscal Years 2000-2005*.

¹³ David A. Kessler, *A Question of Intent* (2001), at 18-19.

I. PURPOSE AND METHODOLOGY

On November 17, 2004, the Government Reform Committee held a hearing into the causes of the flu vaccine shortage that occurred after British regulators acted in October 2004 to shut down a vaccine production facility run by the Chiron Corporation in Liverpool, England.¹⁴ FDA documents released at the hearing showed that FDA field inspectors had found significant violations at the Chiron plant in June 2003 and recommended the initiation of enforcement action, but their recommendation was rejected. The result was that corrective actions were not taken and FDA was caught by surprise when British regulators closed the facility after finding widespread safety violations.¹⁵

Following the hearing, Rep. Waxman wrote to Chairman Davis to propose that the Committee investigate FDA enforcement under the Bush Administration, specifically requesting “attention to cases where career investigators believed official action to protect the public health was warranted but could not proceed.”¹⁶ Chairman Davis agreed, and on March 4, 2005, Chairman Davis and Ranking Minority Member Waxman wrote to FDA to request documents related to enforcement policies and activities at FDA.¹⁷

The Committee requested the following documents:

1. Documents relating to changes in FDA’s enforcement policy since 2001;
2. Documents from the Center on Drug Evaluation and Research and the Center on Biologics Evaluation and Research relating to cases where FDA officials recommended enforcement action but no enforcement action was taken; and
3. A list of all seizures, injunctions, and criminal prosecutions initiated by FDA since 2001, with a summary of outcomes.

In response to the first part of the Committee’s request, FDA provided draft and final versions of the new enforcement policy announced in September 2001 by the Director of the Office of Enforcement. FDA also provided copies of the agency’s “Regulatory Procedures Manual” and a handbook used to train FDA employees on enforcement procedures and policies.

¹⁴ House Committee on Government Reform, Hearing, *The Nation’s Flu Shot Shortage* (Nov. 12, 2004).

¹⁵ House Committee on Government Reform, Minority Staff, *Briefing Memo, FDA Failed to Oversee Vaccine Plant: Summary of FDA Documents* (Nov. 17, 2004).

¹⁶ Letter from Ranking Minority Member Henry A. Waxman to Chairman Tom Davis (Feb. 8, 2005).

¹⁷ Letter from Chairman Tom Davis and Ranking Minority Member Henry A. Waxman to Acting Commissioner Lester Crawford (March 4, 2005).

In response to the second part of the Committee's request, FDA provided 138 case files involving drugs or biological products, dating from early 2001 through April 2005. The documents included files from 18 of 19 district offices across the country.¹⁸ Each of the case files represented an incident where field officials requested enforcement action that was rejected by FDA officials in Washington.

In response to the third part of the Committee's request, FDA provided copies of the agency's "Enforcement Stories" for fiscal years 2001 through 2005. These internal publications, which are intended "to serve as an information source for the FDA's personnel," provide overall data on enforcement actions taken during each year, including warning letters, seizures, injunctions, and criminal prosecutions.

This report is based in large part on a review of the documents provided by FDA. In total, over four thousand pages of documents were submitted by FDA to the Committee and reviewed by the Special Investigations Division in the course of preparing this report.

In addition to reviewing the FDA documents, the Special Investigations Division spoke with and obtained additional information from current and former FDA officials and independent experts. The experts consulted by the Special Investigations Division included Dr. Jerry Avorn, Professor of Medicine at Harvard Medical School; Dr. Michael Wilkes, Vice Dean of Medical Education at the University of California at Davis School of Medicine; and Sammie Young, former Director of Compliance at FDA's Bureau of Biologics and a 29-year veteran of the agency.

Previous reports by the Special Investigations Division have examined enforcement actions by individual divisions within FDA, such as the division responsible for overseeing drug advertising¹⁹ and the center regulating vaccine production.²⁰ This report is the first comprehensive examination of the FDA enforcement record under the Bush Administration.

¹⁸ FDA provided no files from the San Francisco District Office.

¹⁹ House Committee on Government Reform, Minority Staff, *FDA Enforcement Actions Against False and Misleading Prescription Drug Advertisements Declined in 2003* (Jan. 2004).

²⁰ House Committee on Government Reform, Minority Staff, Briefing Memo, *FDA Failed to Oversee Vaccine Plant: Summary of FDA Documents* (Nov. 17, 2004); House Committee on Government Reform, Minority Staff, Fact Sheet, *FDA's Testimony to Congress on the Flu Vaccine Shortage* (Dec. 7, 2004).

II. FINDINGS

The report finds that there has been a dramatic decline in FDA enforcement actions over the last five years. Enforcement statistics show that FDA sent far fewer warning letters and conducted fewer seizures in 2005 than in 2000. One reason for the decline in enforcement actions is revealed in the internal FDA files reviewed in the investigation: FDA officials in Washington repeatedly rejected the recommendations of career field officials urging enforcement actions, even in cases involving death and serious injury.

**“[T]he Food and Drug Administration seems unable and unwilling to step in to protect the American public.”
— Dr. Michael Wilkes, University of California, Davis, School of Medicine**

One independent expert consulted during the investigation, Dr. Jerry Avorn of Harvard Medical School, described the drop in enforcement activity as indicative of “an agency unwilling to exert its regulatory authority in defense of the public’s health.”²¹ According to Dr. Avorn, “Many of us in the medical community have been concerned about a growing laxity in FDA’s surveillance and enforcement procedures.”²² He also cited a “dangerous decline in regulatory vigilance” and said that FDA exhibits an “obvious unwillingness to move forward even on claims from its own field offices which it acknowledged were worrisome.”²³

Another expert, Dr. Michael Wilkes, the Vice Dean at the University of California, Davis, School of Medicine, stated that FDA has “systematically ignored District Field Officers and regularly overridden their explicit and well documented concerns about drug safety and public health.”²⁴ According to Dr. Wilkes:

Today the snake oil salesman need not travel in horse and cart nor even in automobiles — they use the internet and the mail to make the same outrageous claims with products that contain sometimes dangerous ingredients and often inert useless ingredients. And the Food and Drug Administration seems unable and unwilling to step in to protect the American public.²⁵

These views were echoed by Sammie Young, the former FDA enforcement official, who wrote:

²¹ Letter from Dr. Jerry Avorn to Representative Henry A. Waxman (May 25, 2006).

²² *Id.*

²³ *Id.*

²⁴ Letter from Dr. Michael Wilkes to Rep. Henry A. Waxman (June 10, 2006).

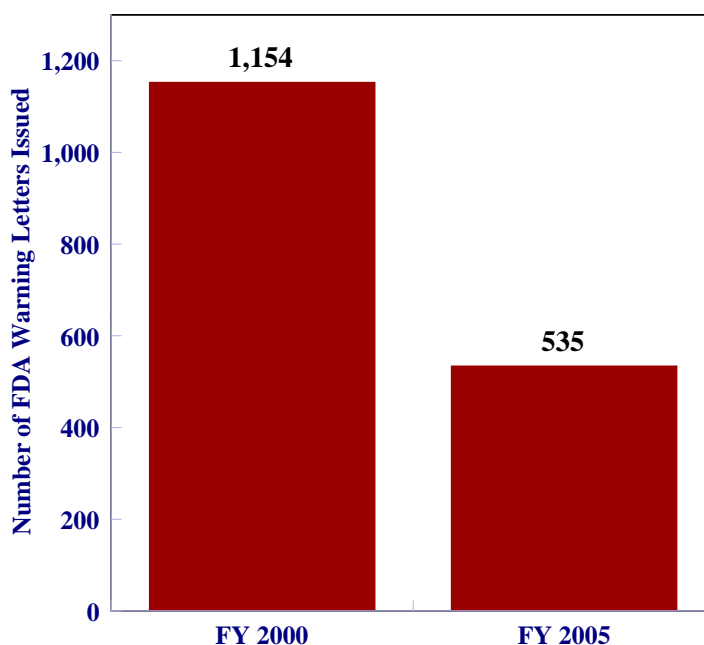
²⁵ *Id.*

I have serious concerns about how FDA is currently fulfilling its enforcement responsibilities. These documents involve many cases where FDA headquarters overruled the clear and thorough recommendations of field offices to take enforcement action against a firm. In most of these instances, the explanation given by FDA headquarters for the decision was inadequate or unreasonable. ... Overall, these documents tend to represent a culture of disapproval or a lack of full dedication to the protection of public health.²⁶

A. Enforcement Has Declined Under the Bush Administration

Agency enforcement efforts have fallen sharply under the Bush Administration. The overall number of warning letters issued by the agency decreased from 1,154 in fiscal year 2000 to 535 in fiscal year 2005, a drop of over 50%. Figure 1.

Figure 1: FDA Enforcement Has Declined by Over 50% Since 2000



The decline in enforcement has occurred throughout the different agency centers. The Center for Drug Evaluation and Research, which is responsible for regulating

²⁶ Letter from Sammie Young to Representative Henry A. Waxman (June 23, 2006)

prescription and over-the-counter drugs, issued 39% fewer warning letters in 2005 (79 letters) than in 2000 (130 letters). The Center for Food Safety and Applied Nutrition, which is responsible for food safety, issued 45% fewer warning letters in 2005 (183 letters) than in 2000 (335 letters). And the Center for Veterinary Medicine, which oversees animal drugs, issued 54% fewer in 2005 (54 letters) than in 2000 (118 letters).

The FDA center with the largest decline in warning letters is the Center for Devices and Radiological Health, which is responsible for ensuring the safety and effectiveness of medical devices. This Center issued 65% fewer warning letters in 2005 (182 letters) than in 2000 (528 letters). According to Dr. Jerry Avorn, this decline is “striking” because it occurred “during a period ... of growing problems in the safety of devices such as implantable pacemakers and defibrillators.”²⁷

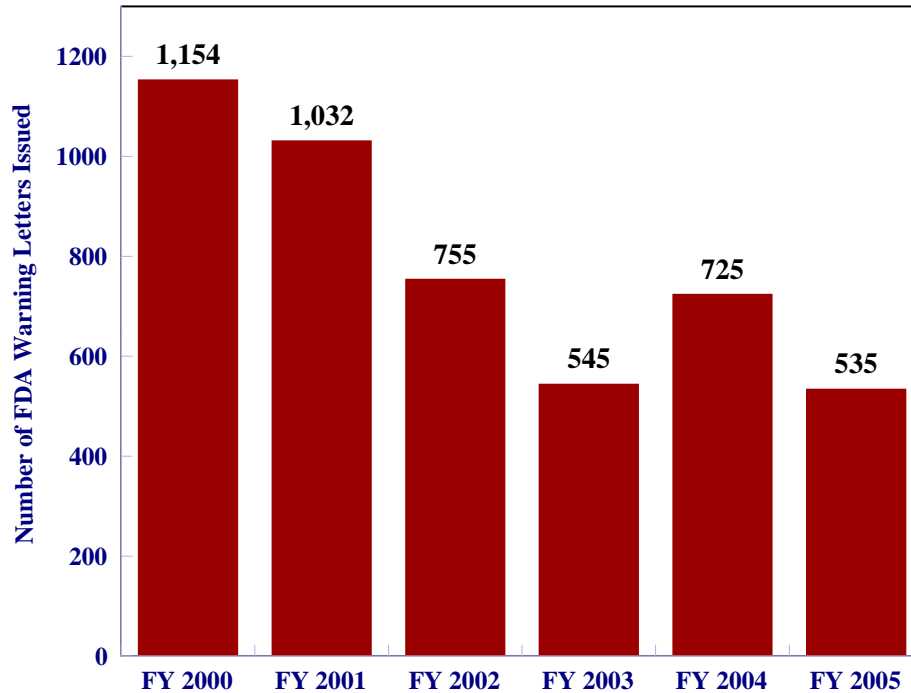
The center with the smallest decline in warning letters is the Center for Biologics Evaluation and Research, which is responsible for regulating products such as blood, tissue, and vaccines. This Center issued 14% fewer warning letters in 2005 (37 letters) than in 2000 (43 letters). Table 1.

Table 1: Enforcement Actions Have Declined In All FDA Centers			
FDA Center	# of Warning Letters Issued		% Decline
	FY 2000	FY 2005	
Devices & Radiological Health	528	182	66%
Veterinary Medicine	118	54	54%
Food Safety	335	183	45%
Drugs	130	79	39%
Biologics	43	37	14%
Total	1,154	535	54%

The decline in the number of FDA warning letters has been consistent throughout the Bush Administration, with the number of letters declining in four of the last five years. The number of warning letters declined by 11% in 2001, 27% in 2002, and 28% in 2003. After increasing slightly in 2004, the number of warning letters again declined (by 26%) in 2005, reaching a 15-year low. Figure 2.

²⁷ Letter from Dr. Jerry Avorn to Rep. Henry A. Waxman (May 25, 2006).

Figure 2: The Number of FDA Warning Letters Has Declined for Four of the Last Five Years



A similar trend characterizes agency seizures. The number of seizures of unsafe products conducted by FDA fell by 44%, from 36 in 2000 to 20 in 2005.²⁸

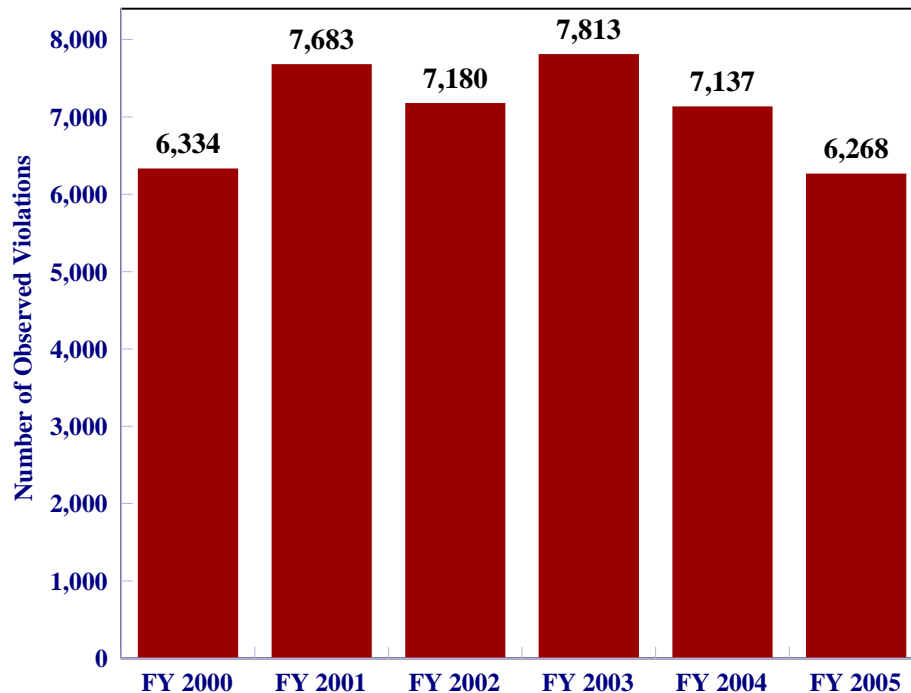
Only one enforcement measure has shown a significant increase over the last five years: the number of FDA-regulated products on the market that had to be recalled increased by 44%, from 3,716 in 2000 to 5,338 in 2005. Since one of the goals of an enforcement system is to deter violations and keep dangerous products off of the market, the increase in recalls is not a hallmark of effective enforcement.

Increased compliance by manufacturers does not appear to account for the decline in FDA enforcement activity under the Bush Administration. Whenever FDA field inspectors observe violations during an inspection, the inspectors give the firm a notice to inform them of the violations observed. These notices, referred to as “483 forms,” are an indication of the number of violations observed during a given year. In 2000, FDA issued 6,334 such forms. The number of “483 forms” issued was higher for the next four

²⁸ The agency’s criminal enforcement actions also have declined over the past five years, with convictions dropping by 27% from 353 in 2000 to 275 in 2005. Arrests also fell from 421 in 2000 to 383 in 2004, but spiked upwards to 535 in 2005. During this period, civil money penalties were consistently rare, with only one imposed in both 2000 and 2005.

years: 7,683 in 2001; 7,180 in 2002; 7,813 in 2003, and 7,137 in 2004. In 2005, FDA issued 6,268 “483 forms,” almost identical to the number issued in 2000. See Figure 3.

Figure 3: The Number of Violations Observed by FDA Inspectors Has Not Declined



B. Enforcement Recommendations of Field Offices Are Often Rejected

Internal FDA documents indicate that in at least 138 cases involving drugs or biological products over the last five years, FDA failed to take enforcement actions recommended by the agency’s own field inspectors. The problems identified by inspectors fell into a number of different areas. They included 110 cases where drug labeling and new drug application requirements were violated; 99 cases where manufacturing standards were violated; and 2 cases where firms failed to report adverse drug events to FDA. Many of the files (over 40%) involved multiple types of violations.

In nearly half of these cases (67 cases), FDA took no enforcement action at all against the firm identified by field inspectors. In the remaining cases, the agency took action that was weaker than recommended by the field inspectors.

In 32 cases, the FDA field inspectors recommended that FDA issue a warning letter, seize the product, or seek a court injunction, but FDA ended up sending only an untitled letter. Because an untitled letter does not require a written response, warn that additional enforcement action may follow if the firm does not correct its violations, or mandate a follow-up inspection, the effect of this downgrade in the enforcement response was to minimize the violations and lessen the likelihood of voluntary compliance.²⁹

In 20 cases, the FDA field inspectors recommended that FDA issue an untitled letter or a warning letter, seize the product, or seek a court injunction, but FDA rejected the recommendations and opted instead to hold a “regulatory meeting.” When a regulatory meeting is the outcome, no formal action is taken but firm representatives meet with FDA personnel to discuss the violations and potential corrective measures.

In rejecting a field office’s recommendation for issuance of a warning letter, an FDA official in Washington wrote, “the recurring deviations documented suggest that it would be more appropriate to issue a Warning Letter, but I realize that too much time has elapsed since FDA’s inspection.”

In five cases, FDA placed the recommendations into temporary abeyance. Although FDA provided no information on the final outcome of these cases, it appears that no official action was taken against any of these firms.³⁰

In many of the cases, FDA officials in Washington undermined the efforts of field officials through extended delays in acting on the enforcement recommendations. In one case, the agency took nearly two years to respond to a field inspector’s recommendation for a warning letter. In nine cases, FDA took over a year to respond to the field office recommendations. FDA took no action for seven months on a recommendation involving repeated violations by a blood products licensing

firm. In rejecting the field office’s recommendation for issuance of a warning letter, an FDA official in Washington wrote: “the recurring deviations documented suggest that it would be more appropriate to issue a Warning Letter, but I realize that too much time has elapsed since FDA’s inspection.”³¹

²⁹ FDA, *Regulatory Procedures Manual*, Chapter 4 (March 2004).

³⁰ In at least one case, FDA asked a field office to withdraw its recommendation rather than have it denied. In that case, the field office declined to withdraw, but it is possible that such withdrawal was suggested in other cases, leaving no record of the initial recommendation.

³¹ E-mail from FDA Compliance Officer to Pyramid Biologicals (Nov. 4, 2004).

In multiple cases, enforcement recommendations were rejected where actual harm, including death, resulted from the violations. Examples of these cases are described below.

1. MEDICAL GAS TANK ERRORS

On February 23, 2001, FDA field inspectors recommended that the agency initiate criminal proceedings against BOC Gases, a leading medical gas supply company, after the improper labeling and distribution of industrial nitrogen as medical oxygen resulted in four deaths. Under the Federal Food, Drug and Cosmetic Act, the first step in FDA criminal proceedings is a “section 305” hearing before FDA at which the company is provided an opportunity to appear. The recommendation from the district office stated “unless evidence of substantially mitigating circumstances is disclosed ... of a nature which would preclude prosecution, we intend to proceed with a prosecution recommendation.”³²

This case began on November 29, 2000, when BOC Gases delivered four tanks of gases to a nursing home in Bellbrook, Ohio. All four of these tanks were sold as containing medical oxygen. One tank, however, contained industrial grade nitrogen.³³

On December 6, 2000, the tank containing nitrogen was connected to the nursing home’s oxygen delivery system. The next morning, according to FDA, “several (10) patients started going into full arrest under suspicious circumstances. ... [A] total of four victims had died within 10 days after the mix-up occurred.”³⁴

FDA’s Cincinnati District Office began an investigation of the incident on December 8, 2000. The FDA field inspectors found numerous “significant deficiencies” involving BOC Gases, including the failure to establish appropriate procedures for identification, storage, and handling of the gas tanks; the failure to establish appropriate storage spaces to prevent delivery of the wrong type of gas; the failure to maintain adequate controls of the delivery process; the failure to provide adequate training for drivers; and the failure to adequately train personnel.³⁵ The investigators also reported that this was not an isolated mistake, but that “many of these conditions ... are a corporate-wide problem.”³⁶

³² FDA, Memo from Cincinnati District to Director, Office of Compliance, CDER, *Citation Recommendation for 305 Notice*, The BOC Group, at 11 (Feb. 23, 2001).

³³ The delivery ticket represented the nitrogen tank as containing medical grade oxygen. The actual tank bore an oxygen label with a nitrogen label placed on top of the oxygen label. *Id.* at 1, 8.

³⁴ *Id.* at 5.

³⁵ *Id.* at 6-8.

³⁶ *Id.* at 8. In fact, on the same day that Cincinnati field staff began their investigation, the New Orleans District Office issued a warning letter to BOC Gases for violations found in an Alabama facility, citing similar deficiencies in quality control and employee training. FDA, *Warning Letter to John L. Walsh, BOC Gases*, at 1 (Dec. 8, 2000).

The Cincinnati District Office concluded that “these deaths are directly attributable to ... deficiencies” at BOC Gases.³⁷ As a result, the district office recommended the initiation of criminal proceedings for a violation of section 301 of the Federal Food, Drug, and Cosmetic Act, which prohibits the “adulteration and misbranding” of drugs and medical devices.³⁸

Over 18 months later, an additional review by FDA’s Division of Manufacturing and Product Quality also recommended prosecution, noting that “the firm fails to understand the significance of the violations” and was “arrogan[t] regarding not only industry practice but the current Good Manufacturing Practices.”³⁹

Despite these recommendations, FDA took no action on this case until October 9, 2002, almost two years after the deaths caused by the mislabeled nitrogen. At this point, FDA declared that the agency was “unable to make a criminal referral” as a result of “several longstanding issues.”⁴⁰ In the end, FDA took no enforcement action of any kind.

2. IMPROPER BLOOD TRANSFUSIONS

On February 2, 2005, FDA’s San Juan District Office recommended that Hospital Damas, a hospital and blood bank in Ponce, Puerto Rico, receive a warning letter as a result of errors in a blood transfusion that resulted in the death of a patient.

³⁷ FDA, Memo from Cincinnati District to Director, Office of Compliance, CDER, *Citation Recommendation for 305 Notice*, The BOC Group, at 1 (Feb. 23, 2001).

³⁸ *Id.* At the time this recommendation was made, the State of Ohio had indicted BOC Gases on charges of reckless homicide. The field office reviewed and thoroughly evaluated the impact of the state case and recommended pursuing federal criminal action at the same time, observing that “no individuals, including the corporate officials, were indicted” and “the indictment of BOC Gases on charges of reckless homicide does not provide assurances that the firm will be convicted and may not even stand trial.” *Id.* at 9. The elements of the Ohio crime of reckless homicide are significantly different from the elements of adulteration and misbranding under the Federal Food, Drug, and Cosmetic Act. Under Ohio law, reckless homicide requires evidence that a person or company acted “with heedless indifference to the consequences [and] perversely disregarded a known risk that his conduct [was] likely to cause a certain result.” 29 O.R.C. §2901.22. By contrast, the charges of adulteration and misbranding recommended by the district office do not require evidence of indifference or any other state of mind. Instead, the federal law allows criminal penalties to be imposed for all violations. If offenses are committed “with the intent to defraud or mislead,” the penalties imposed are higher. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 333(a)(2).

³⁹ FDA, Memo from Case Management and Guidance Branch to Director, Office of Compliance Management and Operations, *DOC 120125 Nitrogen Sold As Medical Oxygen*, at 2, 4 (July 8, 2002). At the time this second recommendation was made, the state case against BOC Gases had been dismissed. Notwithstanding this dismissal, FDA’s Division of Manufacturing and Product Quality concluded that a federal case remained “supportable based on its technical merits and as a punitive action.” FDA, Memo from Director, Division of Compliance Management and Operations, to Deputy Chief Counsel for Litigation, Office of Chief Counsel, *FDC-66894 Prosecution Recommendation (DOC 120125 Nitrogen)*, at 6 (July 15, 2002). In supporting the recommendation, division staff noted that the state case had involved substantially different charges, had been dismissed on questionable legal grounds, and did not preclude federal charges under Justice Department policy. *Id.* at 5-6.

⁴⁰ E-mail from FDA Compliance Officer to Director of Compliance, *FDC 66894: BOC Prosecution* (Aug. 5, 2003).

In this case, FDA field inspectors identified “three significant violations” that resulted in death or endangerment of patients.⁴¹ The inspectors found that on August 31, 2004, two type-A positive blood units were transfused to a type O positive patient, who died the next day. Upon further investigation, the FDA officials found that similar mistakes occurred in June 2001 and in January 2004, each time resulting in severe risk to patient health. The FDA inspectors concluded that there was “no indication that the firm is implementing adequate corrective actions to prevent re-occurrence” of the problems.⁴²

During their inspection of the facility in September and October 2004, the FDA field inspectors found that the blood bank “failed to follow written standard operating procedures” necessary for transfusions.⁴³ The violations identified by the inspectors

When a blood bank inspection reported “three significant violations” that resulted in death or endangerment of patients, the Office of Compliance in the Center on Biologics chose not to issue a warning letter, saying the problems did “not represent or suggest there are systemic problems with the firm’s blood bank operation.”

included failure to verify patient information, medical orders, and information on the product labels; failure to perform a thorough investigation; failure to adequately train employees; and failure to report consistent information to FDA.

On February 2, 2005, the field office sent the FDA’s Center for Biological Evaluation and Research a recommendation that the blood bank receive a warning letter.⁴⁴ In its recommendation, the district office reported “significant objectionable conditions” at the blood bank and multiple staff failures to follow standard operating procedures in the handling, release, and distribution of blood and blood products. The recommendation also stated that the district office “does not have any indication that the firm is implementing adequate corrective actions to prevent re-occurrence of objectionable conditions.”⁴⁵ In a draft warning letter, the district office wrote that despite the corrective actions proposed by Hospital Damas, “[t]his agency still has serious concerns with [the hospital’s] blood and blood components distribution operations.”⁴⁶

⁴¹ FDA, Memo from Compliance Officer, San Juan District Office, to Chief, Division of Case Management, CBER, *Request for Concurrence: Warning Letter Recommendation* (Feb. 2, 2005).

⁴² *Id.* at 2.

⁴³ FDA, *Draft Warning Letter to Mariano McConnie Angel, Hospital Damas, Inc.* (Feb. 2005).

⁴⁴ FDA, Memo from Compliance Officer, San Juan District Office, to Chief, Division of Case Management, CBER, *supra* note 41 (Feb. 2, 2005).

⁴⁵ *Id.* at 2.

⁴⁶ *Draft Warning Letter to Mr. Mariano McConnie Angel, Hospital Damas Inc., supra* note 43.

On March 10, 2005, the Office of Compliance in the Center on Biologics chose not to issue a warning letter. In a nonconcurrency statement, the Center wrote that the problems found by FDA inspectors “[do] not represent or suggest there are systemic problems with the firm’s blood bank operations, but describe a single, isolated event ... and the firm’s proposed actions appear adequate to address the issues.”⁴⁷ The compliance office also stated that the blood bank’s failure to conduct an adequate and complete investigation was “not significant enough to warrant regulatory action.”⁴⁸

During same period, the blood bank was also being investigated by the Centers for Medicare and Medicaid Services, which fined the blood bank \$16,100 in October 2004 for issues related to the competency and training of operating room personnel.⁴⁹

3. “HANGOVER FORMULA”

On October 19, 2001, FDA’s Denver District Office recommended that Vale Enterprises, the marketer of a product known as “Hangover Formula,” and Natural Connections Ltd, the manufacturer of the product, receive a warning letter because the product contained a “toxic level of caffeine.”⁵⁰ The district office described the warning letter as “essential.”⁵¹

According to the district office, three individuals took Hangover Formula in July 2001, became ill, and had to be admitted to the emergency room. These individuals suffered from symptoms that included “vomiting, fluctuating pulse, irregular heartbeat, and blurred vision, nausea, and diarrhea,” which the field office said were “consistent with caffeine toxicity.”⁵² The field inspectors also noted that “there may be other cases which have been misdiagnosed” by medical personnel.⁵³

The FDA district office also investigated the composition of the product. The office found that although Hangover Formula was no longer being sold by the company, the firm had prepared a nearly identical formulation for potential distribution. Samples of the initial formulation tested by FDA found between 3.4 and 4.15 grams of caffeine per serving, which is approximately 50 times as much caffeine as in twelve ounce cola and up to 40 times as much caffeine as in over-the-counter products such as NoDoz.

⁴⁷ FDA, Memo from Division of Case Management, CBER, to Compliance Officer, *Warning Letter Recommendation*, at 1 (Mar. 10, 2005).

⁴⁸ *Id.*

⁴⁹ *Id.* at 3.

⁵⁰ FDA, Memo from Compliance Branch to Center for Drug Evaluation and Research, *Vale’s Hangover Formula*, 1 (Oct. 19, 2001).

⁵¹ *Id.*

⁵² FDA, *Proposed Warning Letter to Vale Enterprises* (Oct. 2001).

⁵³ FDA, Memo from Compliance Branch to Center for Drug Evaluation and Research, *supra* note 50, at 2.

According to the FDA inspectors, this is a “toxic level of caffeine”⁵⁴ that “approaches the lower end of the dose range at which death may occur.”⁵⁵

The FDA district office determined that the product met the definition of a drug and was in violation of FDA law because it was dangerous to health when used at the labeled dosage; was an unapproved new drug; contained inadequate directions for use; and had a false or misleading label. In addition, the district office indicated that were the product considered to be a food, it would be in violation of the law because the high levels of caffeine rendered it unfit as a food product.

As a result of these problems, the Denver District Office recommended that a warning letter be sent to both Vale Enterprises and Natural Connections Ltd. The district office also noted that four other products sold by Vale Enterprises were in violation of food or drug law because they failed to contain appropriate labeling information.

FDA’s Office of Compliance in the Center for Food Safety and Applied Nutrition failed to respond to the Denver District Office’s request for a warning letter until February 2003, 16 months after the request was initially sent. The headquarters office refused to take action on the drug-related claims on the rationale that the claims did not meet the statutory definition of a drug. And the office rejected the unsafe food claims because a “hazard analysis” had not been conducted by the agency. The compliance office also indicated that because the Hangover Formula was no longer on the market, such an analysis was “moot.”⁵⁶ As a result, FDA apparently took no further action in this case.

4. OTHER CASES

Two significant cases in the files involve the failure of firms to file required adverse event reports. In one case, FDA field inspectors found that Purdue Pharma failed to report within the required period “twelve serious and unexpected adverse events” related to the company’s epidural painkiller Chirocaine.⁵⁷ These adverse events included “loss of consciousness,” “grand mal convulsion,” “sensory loss,” fecal and urinary incontinence, “hypotension,” and numerous other health problems.⁵⁸ In addition, the inspectors reported that “the firm acknowledged that many instances of potential adverse event information were documented in notes by sales representatives but not reported by them.”⁵⁹ Yet in this case rather than send the recommended warning letter, FDA sent the

⁵⁴ *Id.* at 1.

⁵⁵ FDA, Memo from Director, Division of Enforcement, CFSAN, to Director, Denver Office, and Compliance Officer, *Warning Letter Recommendation: Returned to District*, at 3 (Feb. 2003)

⁵⁶ *Id.*

⁵⁷ FDA, Memo from Compliance Officer to Office of Compliance, CDER, *Purdue Pharma LLP: Basis for Warning Letter* (Apr. 13, 2004).

⁵⁸ FDA, Letter to Purdue Pharma (June 10, 2004).

⁵⁹ Memo from Compliance Officer to Office of Compliance, CDER, *supra* note 57, at 2.

firm an untitled letter instead.⁶⁰

In another case, FDA field inspectors found that Braintree Laboratories failed to inform FDA in a timely fashion of two deaths and other adverse reactions related to its gastrointestinal drug Go-Lytely. According to the field inspectors, the firm had waited several weeks — in one case over a month — to report two consumer deaths and had “incorrectly characterized” ten other adverse drug events: severe hives and facial swelling; rectal bleeding; vomiting; and several other events that required emergency room treatment.⁶¹ Yet FDA again rejected the recommendation for a warning letter, providing no explanation for its decision.⁶²

The FDA documents also show that in some cases, the agency’s failure to take enforcement action resulted in continued noncompliance that posed a health risk to consumers. For example, Answered Prayers continued to market unapproved products containing progesterone and other hormones after FDA rejected a recommended warning letter. In this case, the district office found that the firm distributed the hormone-containing drugs without approval, lied to an FDA employee, and failed to report to FDA or investigate consumer reports of adverse events such as “burning sensations” caused by a vaginal gel sold by the company.⁶³ According to Dr. Wilkes, progesterone-containing products like those sold by Answered Prayers can have “negative effects” when used improperly.⁶⁴

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In another case, FDA rejected district office concerns and allowed a drug firm to continue marketing an over-the-counter asthma treatment, “Neoasma Tablets,” containing theophylline, an ingredient not approved for over-the-counter products.⁶⁵ According to Dr. Wilkes, the product posed a serious medical risk, particularly to children, because theophylline “is well known to have significant and dangerous side effects.”⁶⁶

⁶⁰ FDA, Letter to Purdue Pharma, *supra* note 58.

⁶¹ *Id.*

⁶² FDA, Memo from Compliance Officer to Division of Compliance, CDER, *Braintree Laboratories: Basis for Warning Letter* (May 3, 2004).

⁶³ FDA, Memo from Compliance Officer to Office of Compliance, CDER, *Proposed Warning Letter for Lack of NDA, Answered Prayers, Inc.* (Feb. 28, 2003).

⁶⁴ Letter from Dr. Michael Wilkes to Rep. Henry A. Waxman (June 10, 2006).

⁶⁵ FDA, Memo from Division of New Drugs and Labeling Compliance, CDER to Tarmac Products, *Further Field Action Indicated* (Oct. 14, 2004).

⁶⁶ Letter from Dr. Michael Wilkes to Rep. Henry A. Waxman (June 10, 2006).

C. FDA's Recordkeeping and Case Tracking Practices Are Inadequate

In response to the Committee's document requests, FDA provided 138 case files involving drugs or biological products in which the enforcement recommendations of field offices were rejected by FDA officials in Washington. These 138 case files do not, however, appear to represent all the cases involving these products in which FDA officials in Washington rejected enforcement recommendations.

FDA officials told the Committee that there is no centralized case tracking system within the agency. As a result, to collect documents responsive to the Committee's request, FDA reported that it relied on the personal recollection of various field office employees. FDA was asked to confirm that the documents it provided represented all relevant case files. The agency was unable to do so, saying that the agency does not keep track of the enforcement recommendations made by district offices and their outcome.⁶⁷

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Some of the gaps in FDA's response were readily apparent. This investigation into the FDA enforcement record was started after a Committee hearing in November 2004 revealed that FDA officials in Washington had rejected the recommendation of field inspectors to initiate an enforcement action in 2003 for violations at the Chiron vaccine plant in Liverpool, England.⁶⁸ Yet ironically, these records — which were the only ones the Committee knew definitively to exist before the start of the investigation — were not identified through the "personal recollection" search conducted by FDA and were not provided to the Committee.

Moreover, FDA provided no records involving the Office of Chief Counsel at FDA. This was unexpected because a previous investigation by the Special Investigations Division had attributed a sudden decline in enforcement cases involving misleading drug advertisements to the issuance of a

⁶⁷ Briefing by David Boyer, Assistant Commissioner for Legislation, Steven Niedelman, Assistant Commissioner for regulatory affairs, and David Elder, Director of the Office of Enforcement, FDA, to House Government Reform Committee Staff (Mar. 31, 2006).

⁶⁸ House Committee on Government Reform, Minority Staff, *Briefing Memo, FDA Failed to Oversee Vaccine Plant: Summary of FDA Documents* (Nov. 17, 2004); House Committee on Government Reform, Minority Staff, *Fact Sheet: FDA's Testimony to Congress on the Flu Vaccine Shortage* (Dec. 7, 2004).

controversial change in FDA enforcement policy in September 2001 that required all warning letters and untitled letters to be approved by the Chief Counsel before issuance.⁶⁹

Under the revised FDA procedures, the Chief Counsel is required to “state *in writing* the reason for nonconcurrence” whenever the Chief Counsel objects to an enforcement action.⁷⁰ Yet when FDA was asked explain why no records from the Chief Counsel were provided, FDA staff indicated that the Office of the Chief Counsel does not maintain copies of its decisions on recommendations or even a record of which files it has reviewed.⁷¹

Even when enforcement records were provided to the Committee, they were often incomplete. Many of the case files lacked the initial recommendation letter from the district, the letter of denial from headquarters, or internal headquarters communications about the case.

These recordkeeping and case tracking practices are inadequate and resulted in a haphazard and untimely response to the Committee’s document requests. They also appear to violate the Federal Records Act and its implementing regulations, which require agencies to create and maintain records “sufficient to ... document the formulation and execution of basic policies and decisions and the taking of necessary actions, including all significant decisions and commitments reached orally.”⁷²

⁶⁹ Letter from Rep. Henry A. Waxman to HHS Secretary Tommy Thompson (Oct. 1, 2002). FDA, Office of Enforcement, *Final Procedures for Clearing FDA Warning Letters and Untitled Letters*, 1 (Mar. 5, 2002).

⁷⁰ FDA, Office of Enforcement, *Final Procedures for Clearing FDA Warning Letters and Untitled Letters*, 4 (Mar. 5, 2002) (emphasis in original). Copies of the decision and reasoning also must be sent to the Deputy Director of the Office of Enforcement at a designated email account, named in the Final Procedures as “ORA Warning Letter Nonconcur.” *Id.* These requirements are repeated in FDA’s Regulatory Procedures Manual. FDA, Regulatory Procedures Manual March 2004, Chapter 4, Exhibit 4-1.

⁷¹ Briefing by David Boyer, Assistant Commissioner for Legislation, Steven Niedelman, Assistant Commissioner for regulatory affairs, and David Elder, Director of the Office of Enforcement, FDA, to House Government Reform Committee Staff (Mar. 31, 2006).

⁷² 36 C.F.R. §1222.38.

CONCLUSION

The findings of this investigation reveal FDA's enforcement efforts have been significantly compromised in the last five years. Between 2000 and 2005, the number of enforcement actions taken by FDA has declined precipitously. In many cases, FDA field inspectors have identified serious violations of the law and recommended enforcement action, but FDA has rejected their recommendations.
